REMARKS

Favorable reconsideration of the claims in view of the remarks which follow is respectfully requested.

At the outset, Examiner Brannock and Supervisory Examiner Eyler are respectfully thanked for the recent personal interview at which the undersigned and Dr. Mark Zoller, a lead scientist from Senomyx Inc., the assignee of this application were present. During this interview, Dr. Zoller presented an overview of the technical research that resulted in the discovery of the human T2Rs including hT2R61, that are the subject of this invention. Particularly, Dr. Zoller explained that these sequences were cloned from the human genome, and encode GPCRs that are involved in taste sensation, particularly bitter taste sensation. Dr. Zoller particularly noted that to date 6 different human T2Rs have been shown to specifically respond to bitter ligands. Of particular relevance to the claims at issue in this application, Dr. Zoller noted that hT2R61, upon its cloning by the present Assignee, was reasonably anticipated to be a bitter taste receptor in the T2R family based on (i) its sequence similarity to previously isolated T2R genes from humans and rodents (ii) its expression in taste tissue in association with gustducin (iii) characteristic structure which indicated that it encoded a GPCR and (iv) the fact that at the time of the invention, several other T2R members had been shown in cell-based assays to respond to bitter ligands. Moreover, Dr. Zoller noted that subsequent cell-based assays confirmed that T2R61 specifically responds to nitrosaccharin, a known bitter ligand, that has a similar structure to the sweetener saccharin, a

compound well known to elicit a bitter after taste. In fact, Dr. Zoller noted that based on hT2R61's specific activation by nitrososaccharin, this receptor can be used in cell-based assays to identify compounds that modulate, preferably block, the bitter-taste elicited by saccharin. Dr. Zoller further explained that while not all members of the T2R family have been functionalized to date, including T2R genes disclosed in this application, that the reasonable expectation is that the other T2R member will similarly be shown to be bitter taste receptors in appropriate cell-based assays. Moreover, Dr. Zoller noted that no evidence known to Applicants would cast significant doubt on the inventors' continued belief that the weight of the evidence on filing of this application reasonably suggests that all of the T2R members claimed herein, including hT2R61, encode human taste receptors that respond to bitter ligands.

Additionally, at the interview, the outstanding § 112 enablement and written description rejections, and § 101 rejections were discussed in some detail. It was emphasized that the scope of enablement rejection would be addressed by limiting the claims to nucleic acid sequences that encode a bitter taste receptor that hybridizes to the disclosed hT2R61 nucleic acid sequence under defined stringent hybridization conditions. In fact, all of the pending claims contain these limitations explicitly or based on their dependency from a claim that positively recites these hybridization conditions.

The utility and written description rejections were rebutted on the basis that the overwhelming weight of the evidence [discussed by Dr. Zoller] available at the time of invention reasonably and predictably suggested to the inventors,

skilled experts in their field of endeavor, that the claimed T2R nucleic acid sequences encoded GPCRs which were members of the T2R taste receptor family, which are involved in detecting bitter taste. It was noted that other T2Rs having similar structures, tissue expression profiles had been previously shown to encode bitter taste receptors, and that it was the inventors' reasonable expectation that hT2R61, as well as the other T2Rs disclosed herein, would likewise be proven to be bitter taste receptors in appropriate functional assays. In fact, hT2R61 has been proven to be a bitter taste receptor that specifically responds to a bitter saccharin containing compound (nitrosaccharin).

The Examiners listened to Applicants' arguments and noted that they would thoroughly consider the weight of Applicants' arguments fully when submitted in writing. It is hoped that the Examiner will now properly conclude that the specification contained sufficient information to support the inventors' reasonable expectation that hT2R61, based on its structure, tissue expression profile, and the established functionality of other T2R members, encodes a bitter taste receptor, as recited in the claims under examination herein.

Turning now to the Office Action, the Examiner questioned wherein the nucleic acid sequence and polypeptide recited in SEQ ID NOs:7 and 8 find support in the priority application. The Examiner is respectfully advised that these sequences respectively correspond to the nucleic acid sequences identified as SEQ ID NO:1 and the corresponding conceptual translation thereof contained in Figure 1 of US Provisional 60/247,014 filed November 13, 2000.

The disclosure stands objected to for containing a reference to an embedded hyperlink. This rejection should be overcome based on the present amendment which deletes the only 2 hyperlinks at pages 17 and 37 respectively.

Prior claims 138-140, 146 and 157 were rejected under § 112 second paragraph. These rejections are addressed to the extent they may be applicable to the claims as amended.

Claims 138-140 were objected to as being ambiguous and unclear based on the recitation "Stringent hybridization conditions". This objection is believed to be overcome because the current claims define stringent hybridization conditions as being the specific conditions finding support at page 31, as suggested by the Examiner.

Claims 138-157 were rejected under 35 U.S.C. § 112 first paragraph, as allegedly not adhering to the written description requirement. This rejection is respectfully traversed.

Applicants' position remains that the as-filed application did correctly describe the hT2R61 nucleic acid sequence contained in SEQ ID NO:7 and encoding the polypeptide in SEQ ID NO:8 as being or encoding a taste receptor involved in bitter taste.

As discussed in detail below and at the recent interview, the present inventors, experts in their field, based their correct identification of hT2R61 as encoding a human bitter taste receptor involved in bitter taste, on a number of different parameters which when considered as a whole, made this a reasonable expectation (which has subsequently been proven). (These specific parameters

are discussed in greater detail in the Declaration by Dr. Mark Zoller that accompanies this Reply.)

In particular, as disclosed herein, Applicants cloned the subject hT2R61 nucleic acid sequence from the human genome, sequenced the cloned gene, and appreciated, based its structure that it was a member of the T2R family. Also, in support of this hypothesis, Applicants discerned that the corresponding T2R polypeptide is specifically expressed in taste tissue in association with gustducin, as are other taste receptors. Further, Applicants were aware of functional assays with other T2Rs which provided compelling functional evidence that other T2Rs specifically respond to bitter taste ligands. (*See* Chandrashekar and Adler references cited in the application) Based on this information, considered as a whole, Applicants reasonably concluded that the subject T2R61 DNA encodes taste receptor that is involved bitter taste modalities in humans.

Moreover, and not unexpectedly, the reasonably anticipated function of hT2R61 as a bitter taste receptor has been confirmed by functional studies which substantiate that nitrosacharin, a known bitter taste compound, activates this taste receptor in a functional assay (which type of assay is among the various functional assays specifically disclosed in the application). (Applicants again note that this hT2R61 functional data relating to nitrosaccharin submitted with Applicants' previous Reply).

In response to similar line of argument in the prior Reply, the Examiner maintained the rejection and relied on statements in the Lindemann et al *Nature Neuroscope* 3(2):99-100 (2000) reference, stating that "at present there is no

functional evidence for this proposal". However, the Examiner is respectfully advised that the statement by Lindemann is not probative as this reference was submitted for publication prior to the Chandrashekar et al. and Adler et al. *Cell* 100:703-711 (2000) publication and therefore failed to take into account the functional data contained in these later-publications.

Additionally, the Examiner dismissed the positive teachings of Chandrashekar on the basis that while 11 human T2R clones were tested that only 1 responded to the bitter tastants tested against these human T2Rs. The Examiner suggested that this provided evidence that success [identifying a putative human T2R that responds to a bitter ligand] "seems to be rare in the art". Based thereon, the Examiner alleged that the specification does not reasonably establish that the polypeptide having SEQ ID NO:8 is functional as a bitter taste receptor.

However, this position taken by the Examiner is respectfully traversed. Absolute predictability is not required to meet the written description and "possession" requirement of § 112 first paragraph, rather merely a "reasonable expectation of success." The fact that hT2R61 possesses a high degree of sequence identity with other T2R family members, including several T2Rs which were already demonstrated to encode functional bitter taste receptors, the fact that hT2R61 is specifically expressed by taste tissue, and possesses a characteristic GPCR domain structure taken as a whole provides this reasonable expectation of success. In this regard, the as-filed specification makes specific

reference to Chandrashekar et al (*Cell*) and Adler et al. (*Cell*) publications both of which contain T2R expression data, homology comparisons and functional data substantiating that T2Rs function as bitter taste receptors provides this reasonable explanation of success. Particularly, these references establish that T2Rs are selectively expressed in gustducin-expressing cells, that gustducin couples specifically to T2R loci that correlate to bitter taste, and contain functional data demonstrating that 3 different T2Rs, *i.e.*, hT2R-4, hT2R-8 and mT2R-5 are activated by different bitter ligands, *i.e.,* cycloheximide, denatonium and PROP (6-n-propylthiouracil).

With further respect thereto, it should be noted that the Chandrashekar and Adler publications are incorporated by reference in the as-filed application. Therefore, this application does contain functional data, albeit not functional data relating to hT2R61. Applicants respectfully submit that this functional data relating to 3 different T2R genes, of 2 different species origin, provides evidence that it was reasonable to expect that another member of this gene family, hT2R61, would also function as a bitter taste receptor under appropriate conditions. Further, it was reasonable to expect that functional assays such as are disclosed in this application, when used to screen against different bitter compounds, would result in the identification of bitter ligands that specifically activate hT2R61; such as nitrosaccharin.

With further respect to this argument, it should also be noted that sodium saccharin (typically simply known as saccharin), at the time this application was

filed, while a known sweet compound, was also well known to elicit a bitter after-taste at high concentrations, and moreover, was listed among the taste ligands which were screened against the various T2R expressing clones disclosed in the Chandrashekar reference incorporated by reference. This provides further convincing evidence that the as-filed disclosure would reasonably suggest that saccharin containing compounds would be among the different bitter tastants that potentially would have activated T2R61. (*See* Experimental Procedures at page 710 of Chandrashekar, wherein sodium saccharin is included in the list of screened tastants). While this compound did not activate the particular T2Rs expressed in the reference, under the conditions described therein, it provides further evidence that Applicants were in possession of the subject invention on filing since it was appreciated that bitter compounds such as saccharin containing derivatives potentially would induce the activation of a T2R taste receptor. In fact, functional assays have later shown that the hT2R61 polypeptide disclosed herein, is activated by this nitrosaccharin, a compound possessing a very similar structure to sodium saccharin which elicits a bitter taste. As saccharin compounds were well known at the time of the invention to elicit a bitter taste (*See, e.g.,* Schiffman et al., *Physiol. Behav.* 23(1):1-9 (1979), "Qualitative differences among sweeteners"; Hoover, R., N. Engl. *J. Med.* 302(10):573-5 (1980), "Saccharin-bitter aftertaste?"; Isselbacher, *N. Engl. J. Med.* 296(23):1348-50 (1977), "Saccharin-the bitter sweet"; Schiffman et al, *Brain Res. Bull.* 36(5):505-13 (1995), "Bitterness of sweeteners as a function of concentration") and further given the fact that saccharin's bitter taste had been

earlier correlated to the genetic ability to taste another bitter substance, 6-n-propylthiouracil [identified in the application], this provides additional evidence that the information contained in the specification when considered as a whole provided sufficient information to establish that Applicants were in "possession" of the invention as it related to the nucleic acid sequence, hT2R61, which encodes a human taste receptor involved in bitter taste sensation. Also, another research group (Bufe et al.) has recently shown that saccharin modulates the activity of hT2R61. (*See,* Zoller Declaration ¶ 13 and Bufe et al, Association of Chemorception Sciences April 21-25, 2004, Abstract #191) Based on the foregoing, and further in view of the Zoller Declaration, withdrawal of the § 112 first paragraph rejection based on written description, is respectfully requested.

Claims 138-157 further were rejected under U.S.C. § 101 as lacking utility. Essentially, the rejection is predicated on the same basis as the § 112 rejection, *i.e.,* that the specification purportedly does not establish a utility for hT2R61, because of the absence of functional data in the as-filed application evidencing that this polypeptide responds to specific bitter taste stimuli.

This rejection is respectfully traversed for the same reasons as the § 112 written-description based rejection. Essentially, Applicants note that the as-filed specification teaches that hT2R61 encodes a receptor polypeptide involved in bitter taste detection, and which can be used specifically discloses binding and functional assays that can be used to identify bitter ligands that activate this receptor, and further to identify agonists, antagonists and enhancers of this

human bitter receptor. Moreover, the as-filed application incorporates by reference two Adler and Chandrashekar publications which contain functional assay results that demonstrate that 3 other T2Rs encode bitter taste receptors and respond to bitter taste stimuli. Further, these same publications list a number of different tastants that were screened against the T2Rs expressed therein, and a saccharin derivative, was among those specifically enumerated.

Based thereon, and further based on the evidence and reasons contained in the Zoller Declaration, Applicants respectfully submit that the as-filed specification provided sufficient information to teach one skilled in the art how to use the subject hT2R61 in assays for the identification of bitter ligands that activate this receptor, and other modulators of the activity of this bitter taste receptor. In fact, as substantiated by functional data submitted with Applicant's previous Reply, such functional assays have shown that hT2R61 responds to nitrosaccharin, a compound closely related to sodium saccharin, well known to elicit a bitter taste in humans at elevated concentrations. Also, the Zoller Declaration establishes that hT2R61 is activated by saccharin, a bitter compound specifically mentioned in Chandrashekar and Adler publications incorporated by reference. (*See,* ¶ 13 of Zoller Declaration.) Therefore, Applicants respectfully submit that the disclosed utility of hT2R61 has been validated according to assays described in the as-filed disclosure.

Moreover, contrary to the Office Action, the subject application does not provide a mere "starting point for research". Rather, the subject application

correctly teaches the function (bitter taste receptor) of hT2R61 and also describes in detail functional assays that have been shown to be useful as disclosed, namely such assays detect the identity of bitter compounds that modulate the activity of this receptor.

Also, in response to the Examiner's assertion that bitter taste perception was poorly understood (based on Perruccio and Kleinhous), this statement is respectfully traversed on the basis that this reference does not take into account the later-teachings of Adler (*Cell* 2000) and Chandrashekar (*Cell* 2000), which references contain expression and functional data relating to 3 different T2Rs, as well as gustducin co-expression and coupling experiments that substantiate that related T2Rs indeed function as bitter taste receptors. Therefore, based on the foregoing, withdrawal of the § 101 utility rejection is respectfully requested, on the basis that the specification provides the correct utility of the claimed hT2R61 nucleic acid sequence (bitter taste receptor).

Claims 138-157 further were rejected under 35 U.S.C. § 112 first paragraph as not being enabled. Being that the basis of the rejection is the same as the § 101 and written description rejections, this rejection is respectfully traversed for the same reasons as the § 101 and § 112 written description rejections *supra*. Essentially, for the reasons set forth *supra*, the specification contains sufficient information, when considered as a whole, for one skilled in the art to reasonably conclude that hT2R61 encodes a bitter taste receptor, specifically, the specification provides sufficient information to enable one skilled

in the art to use hT2R61 in assays to identify modulators of this bitter taste receptor, and these functional assays have been shown to be operable as disclosed, namely they have demonstrated that hT2R61 responds to nitrosaccharin, a compound closely structurally related to a bitter compound specifically enumerated as a tastant that was tested in T2R functional assays in a reference incorporated by reference in the as-filed application. As noted previously, saccharin compounds were well-known at the time of the invention to elicit a bitter aftertaste. Therefore, were skilled in the art would have been motivated, as of the time this application was filed, to select bitter compounds related to saccharin for use in hT2R61 functional assays. Therefore, based on the foregoing, withdrawal of the § 112 first paragraph enablement of the rejection is respectfully requested.

Claims 138, 141-157 further stand rejected under 35 U.S.C. § 112 first paragraph on scope of enablement and written description grounds, based on the fact that the claims encompass nucleic acid sequences that encode variants of the T2R61 polypeptide contained in SEQ ID NO:8 which are not sufficiently enabled.

This rejection is respectfully traversed to the extent it may be applicable to the claims as amended. With respect thereto, Applicants note that the current claims only encompass:

(i) nucleic acid sequences encoding hT2R61 having the sequence contained in SEQ ID NO:8;

(ii) nucleic acid sequences that encode variants that possess at least 95%, 96%, 97%, 98% or 99% sequence identity therewith; and

(iii) nucleic acid sequences that hybridize to hT2R61 under defined stringent hybridization conditions and which encode a bitter taste receptor.

Applicants respectfully submit for the reasons set forth *supra*, that a skilled artisan would, based on the teachings of this application, be motivated and able to use the exemplified hT2R61 nucleic acid sequence in functional assays to identify bitter ligands such as saccharin that modulate the activity of this receptor. This argument is substantiated by functional data provided with Applicants' previous Reply and by the Zoller Declaration provided herein which establishes that additional functional data demonstrates that hT2R61 is activated by bitter (saccharin) compounds. Once such ligands were identified, it further would be within the level of skill of the ordinary artisan to select DNAs that hybridize to the subject DNA according to the recited stringent hybridization conditions, or to obtain variants of the subject nucleic acid sequences that encode polypeptides having at least 95%, 96%, 97%, 98% or 99% sequence identity to the hT2R61 polypeptide contained in SEQ ID NO:8, and to identify those variants which also respond to bitter ligands such as nitrosaccharin and sodium saccharin that modulate the activity of hT2R61. This experimentation would not rise to the level of undue experimentation based on the teachings of this application. Moreover, there would be a reasonable expectation of success based on the fact that functional alleles of different T2Rs

were already known to exist and to correlate to bitter taste phenotypic differences.

While the Examiner is correct that only a single nucleic acid sequence is actually exemplified, it is reasonable to expect that polypeptides possessing substantial sequence identity with the polypeptide contained in SEQ ID NO:8, *e.g.,* having at least 95% sequence identity thereto, will function as bitter taste receptors and bind bitter ligands comparably to hT2R61.

Therefore, withdrawal of the § 112 scope of enablement and written description rejections are respectfully requested.

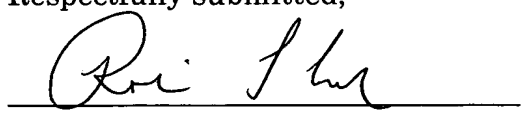
Based on the foregoing, the application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited.

However, if any issues remain outstanding after consideration this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #10033754075US).

Respectfully submitted,

May 14, 2004



Robin L. Teskin
Registration No. 35,030

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
304983

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/825,882	Confirmation No.	: 3758
Applicant	: JON ADLER		
Filed	: April 5, 2001		
TC/A.U.	: 1646		
Examiner	: M Brannock		
Docket No.	: 100337.54075US		
Customer No.	: 23911		
Title	: T2R TASTE RECEPTORS AND GENES ENCODING SAME		

DECLARATION OF MARK ZOLLER, Ph.D.

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mark Zoller, Ph.D., declare and state as follows:

(1) That I have been employed by Senomyx, Inc. from March 2000 to the present date. My title is Chief Scientific Officer and Senior Vice President of Research.

(2) That I am an expert in the subject matter claimed in the above-identified application which relates to human G protein coupled receptors (human GPCRs) that are members of a taste receptor family involved in bitter taste sensation and which are referred to in this application and by the relevant scientific community as T2Rs.

(3) That my expertise in the relevant technology is substantiated by my curriculum vitae which is attached as an exhibit to this declaration.

(4) That I am familiar with the file history in the above-identified patent application including the most recent Office Action. Additionally, I attended in February of this year an interview with Examiner Brannock and Supervisory Examiner Eyler wherein the outstanding objections and rejections were discussed. Based thereon, it is my understanding that the

Examiner has suggested that it was not reasonably predictable from the as-filed application and the then-state of the art relating to taste receptors, and specifically T2R members, that the DNA sequence having SEQ ID NO: 7, encoding the polypeptide contained in SEQ ID NO: 8, also referred to as hT2R61, would have been shown to encode a human taste receptor involved in bitter taste sensation. That based on the following, I respectfully disagree:

(5) That as of the date of this invention, a human T2R referred to as human T2R1 and having a sequence related to hT2R61 had been identified in the human genome and found to be linked with bitter taste. (*See, Adler et al.*, "A novel family of mammalian taste receptors"; *Cell* 100(6):611-8 (March 17, 2000)). This discovery provided the first experimental evidence as to the function of T2R members in bitter taste.

(6) That as of the date of invention, the existence of a family of T2Rs comprised in both rodent (rat and mouse) genomes and the human genome had been known (*Adler et al* (*Id.*)).

(7) That upon the discovery of T2R1, this nucleic acid sequence was used as a probe to identify related T2Rs in rodent and human genomes. In fact, all sequences which were identified using T2R1 encoded GPCRs which are well known to be ligand activated receptors.

(8) That the closest sequence homology of the identified human gene sequences, as well as the T2R sequences disclosed in this application, including hT2R61, were to other T2R members and therefore it was reasonable for the inventors of this application to conclude that these gene sequences encoded GPCRs involved in bitter taste.

(9) That expression data further evidenced that these T2R members were expressed in a subset of taste cells, and were expressed in different cells compared with T1R1 and T1R2-expressing cells (respectively umami and sweet receptors). This result further reasonably suggested to the inventors that T2Rs were responsible for a taste modality distinct from sweet

or umami. Further, we reasonably concluded that the identified T2Rs, including T2R61, were involved in bitter taste, and not salty or sour taste, because the conventional thinking in the taste receptor scientific community at the time of invention and now is that salty and sour taste modalities are regulated by ion channels and not GPCRs.

(10) That the role of T2R members in bitter taste was further supported by experimental data that demonstrated that T2Rs are expressed in cells in association with the G protein gustducin, previously shown by mouse knock out data to be involved in bitter taste. (Wong et al., "Transduction of bitter and sweet taste by gustducin"), *Nature* 381 (658):796-800 (1996)).

(11) That it had been further shown as of the date of invention with other related T2R members that T2Rs are activated by bitter tastants (Chandrashekar et al., *Cell* 100(6):703-11 (March 17, 2000)). Specifically, it was reported by Chandrashekar et al., that mouse T2R5 responded to the bitter ligand cycloheximide and that human T2R4 responds to the bitter ligand denatonium.

(12) That the human T2R members disclosed in this patent application (which were identified in the human genome) were also identified subsequently by another academic lab and were similarly predicted to encode bitter taste receptors (Conte et al., *Cytogenet. Genome Res.* 98(1): 43-53 (2002)). Therefore, there is a consensus in the relevant scientific community that the subject human T2R members, including hT2R61, encode bitter taste receptors. Also, the location and organization of T2Rs in the genome is consistent with gene duplication events leading to gene expression and hence the reasonable expectation that the various T2R members encode functional bitter taste receptors.

(13) That the reasonable expectation as to the functional role of T2R61 in bitter taste is further supported by subsequent ligand data showing that human T2R61 is activated by the bitter ligand nitrosaccharin. Additionally, the function of T2R61 in bitter taste is further evidenced by recent data reported by another research group (Bufe et al.) which showed that human T2R61 (referred to by the Bufe group as human TAS2R44) is activated by the sweetener saccharin, a compound also well known to elicit a bitter taste at elevated concentrations (Bufe et al., "Deorphanization and functional SNP analysis of TAS2R Bitter Taste Receptor", Association of Chemorception Sciences (AChems), Meeting April 21-25, 2004, Abstract #191) In fact, saccharin was among the sweet and bitter ligands mentioned in the Adler et al. (*Id.*) and Chandrashekar et al. (*Id.*) publications incorporated by reference in this application.

(14) That other T2Rs have been shown to respond to bitter ligands as predicted by the inventors of this application. Particularly, T2R16 has been shown to respond to salicin, a bitter ligand, using an assay system described in the above-identified Senomyx patent application (Bufe et al., "The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides", *Nat. Genet.* 32(3):397-401.).

(15) That it is my expert opinion that the above-information considered cumulatively along with the information contained in the above-identified Senomyx patent application supports a conclusion that it was entirely reasonable to anticipate that T2R61 would be shown in bitter ligand functional and binding assays to encode a bitter taste receptor, as correctly disclosed in the Senomyx patent application at issue.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Mark Zoller, Ph.D.
Chief Scientific Officer and Senior Vice President of Research

DATE SIGNED: May 13, 2004

CURRICULUM VITAE

Mark J. Zoller

Personal

Address:	Senomyx, Inc. 11099 N. Torrey Pines Road La Jolla, CA 92037
Phone:	858 646-8307 (wk)
Fax:	858 404-0750 (wk fax)

Education

1971-1975	B.A., Chemistry, 1975, Pomona College, Claremont, CA.
1975-1980	Graduate student with Dr. Susan S. Taylor Department of Chemistry, University of California, San Diego M.S., 1977; PhD., 1980

Professional Experience

1981-1983	Post-doctoral research with Dr. Michael Smith, Nobel Laureate Department of Biochemistry, School of Medicine University of British Columbia, Vancouver, B.C.
1983-1988	Senior Staff Investigator Cold Spring Harbor Laboratory, New York
1988-1992	Senior Scientist Department of Protein Engineering Genentech, Inc, South San Francisco, CA.
1989-	Adjunct assistant professor Department of Pharmaceutical Chemistry School of Pharmacy, UCSF, San Francisco, CA
1992-1994	Director, Molecular Biology ARIAD Pharmaceuticals, Cambridge, MA
1994- 1998	Vice President, Drug Discovery - Signal Transduction ARIAD Pharmaceuticals, Cambridge, MA
1998 - 2000	Scientific Director, Hoechst-ARIAD Genomics Center Senior Vice President, Genomics ARIAD Pharmaceuticals, Cambridge,
2000 -	Senior Vice President, Research and Chief Scientific Officer Senomyx, Inc., La Jolla, CA

BIOGRAPHICAL SKETCH -- Mark J. Zoller, Ph.D

Dr. Zoller joined Senomyx in March 2000 as Vice President, Research to work with renown textbook author and scientist, Professor Lubert Stryer, who serves as Senomyx' Chief Scientific Officer. Senomyx is a newly formed biotech company, dedicated to the discovery of novel molecules that modulate taste and olfaction. The company was formed to exploit recent advances in chemosensory genomics for the development of novel flavor and fragrance molecules for consumer products.

Prior to coming to Senomyx, Dr. Zoller held a number of scientific management positions at ARIAD Pharmaceuticals in Cambridge, Massachusetts, most recently as Scientific Director of the Hoechst-ARIAD Genomics Center and Senior Vice President, Genomics, ARIAD Pharmaceuticals. Previously, Dr. Zoller was a Senior Scientist in the Protein Engineering Department at Genentech, where he used protein engineering technologies to create a series of second-generation tissue plasminogen activators (t-PAs). Dr. Zoller's work led to one of these proteins being developed into the recently approved drug, Tenecteplase. Prior to joining Genentech, Dr. Zoller was a Senior Scientist at the Cold Spring Harbor Laboratory. There he did research on protein kinases using yeast molecular genetics, and taught the Advanced Molecular Cloning course from 1983 to 1987.

Dr. Zoller received his Ph.D. in Chemistry in 1980 from the University of California, San Diego working in the laboratory of Dr. Susan Taylor. Dr. Zoller's thesis characterized the structure and function of cAMP-dependent protein kinase. Having trained in a protein chemistry lab, in 1981 Dr. Zoller did post-doctoral research in the laboratory of Nobel Laureate, Professor Michael Smith in Vancouver, British Columbia. There he developed improved methods for oligonucleotide-directed mutagenesis. Since 1989, Dr. Zoller has been an Adjunct Assistant Professor in the Department of Pharmaceutical Chemistry at University of California, San Francisco. He has published over 40 scientific papers, holds 10 issued patents on second generation t-PA, is on the editorial boards of Protein Engineering, and co-authored a molecular biology textbook entitled Recombinant DNA with Nobel Laureate James D. Watson, along with Michael Gilman and Jan Witkowski, Director of the Banbury Center at the Cold Spring Harbor Laboratory. The textbook is widely used undergraduate and graduate molecular biology courses and has sold over 100,000 copies to date.

PUBLICATIONS

1. Zoller, M.J., A. R. Kerlavage, and S.S. Taylor (1979). Structural Comparisons of cAMP-dependent Protein Kinases I and II From Porcine Skeletal Muscle. J. Biol. Chem. 254: 2408-2412.
2. Zoller, M.J. and S.S. Taylor (1979). Affinity Labeling of the Nucleotide Binding Site of the Catalytic Subunit of cAMP-dependent Protein Kinase Using p-fluorosulfonyl-benzoyl-5' Adenosine. J. Biol. Chem. 254: 8363-8368.
3. Zoller, M.J., N.C. Nelson and S.S. Taylor (1981). Affinity Labeling of cAMP-dependent Protein Kinase with p-fluoro-sulfonylbenzoyl 5' Adenosine: Covalent Modification of Lysine-71. J. Biol. Chem. 256: 10837-10842.
4. Hathaway, G.M., M.J. Zoller and J.A. Traugh (1981). Identi-fication of the Catalytic Subunit of Casein Kinase II by Affinity Labeling with 5'-p-fluorosulfonylbenzoyl Adenosine. J. Biol. Chem. 256: 11442-11446.
5. Taylor, S.S., A.R. Kerlavage, N.C. Nelson, S. Weldon, and M.J. Zoller (1982). Use of HPLC in Characterizing Nucleotide Binding Sites and Antigenic Determinants in cAMP-dependent Protein Kinase. In Methods in Protein Sequence Analysis (M. Elziner, ed.). Humana Press, Inc., Clifton, New Jersey.
6. Winter, G., A.R. Fersht, A.J. Wilkinson, M.J. Zoller, and M. Smith (1982). Redesigning Enzyme Structure by Site Directed Mutagenesis: tyrosyl-tRNA Synthetase and ATP Binding. Nature 299: 756-758.
7. Zoller, M.J., and M. Smith (1982). Oligonucleotide-directed Mutagenesis Using M13-derived Vectors: An Efficient and General Procedure for the Production of Point Mutations in Any Fragment of DNA. Nucleic Acids Res. 10: 6487-6500.
8. Zoller, M.J., and M. Smith. (1983). Oligonucleotide-directed Mutagenesis of Cloned DNA Fragments Using M13-derived Vectors. In Methods in Enzymology, Recombinant DNA, Part II, Vol. 100 p. 468- 500. (R. Wu, L. Grossman, and K. Moldave, eds.).
9. Weiffenbach, B., D. Rogers, J. Haber, M. Zoller, D. Russell, and M. Smith. (1983). Deletions and Single Base Changes in the Yeast Mating Type Locus That Prevent Homothallic Mating Type Conversions. Proc. Natl. Acad. Sci. USA: 80: 3401-3405.
10. Weinmaster, G., M.J. Zoller, M. Smith, E Hinze, and T. Pawson (1984). Mutagenesis of Fujinami Sarcoma Virus: Evidence that tyrosine phosphorylation of p130 gag-fps modulates its biological activity. Cell 37: 559-568.
11. Zoller M.J. and M. Smith (1984). Oligonucleotide-directed mutagenesis: A simple method using two oligonucleotide primers and a single-stranded DNA template. DNA 3: 479-488.
12. Weinmaster, G., Zoller, M.J., and Pawson, T. (1986) A lysine in the ATP-binding site of P130gag-fps is essential for protein-tyrosine kinase activity. EMBO J. 5:69-76.
13. Cool, D.E., Edgell, C.S., Louie, G.V., Zoller, M.J., Brayer, G.D., and Mac Gillivray, R.T.A. (1985). Characterization of human blood coagulation factor XII cDNA: Prediction of the primary structure of factor XII and the tertiary structure of beta-factor XIIa. J. Biol. Chem. 260:13666-13676.
14. Russell, D.W., Jensen, R., Zoller, M.J., Burke, J., Errede, B., Smith, M., and Herskowitz, I. (1986). Structure of the Saccharomyces cerevisiae HO gene and analysis of its upstream regulatory region. Mol. Cell. Biol. 6:4281-4294..
15. Zoller, M. and Smith, M. (1987) Oligonucleotide directed mutagenesis using two primers and a single stranded DNA template. Methods Enzymol. Vol 154.
16. Zoller, M.J. Methods for protein mutagenesis molecular biology. pp. 97-119, in "Methods in Protein Analysis". The Humana Press, 1987.

17. Broek, D., Toda, T., Michaeli, T., Levin, L., Birchmeier, C., Zoller, M., Powers, S., and Wigler, M. (1987) The S. cerevisiae CDC25 gene product regulates RAS/adenylate cyclase pathway. Cell 48:789-799.
18. Toda, T., Cameron, S., Sass, P., Zoller, M., Scott, J.D., McMullen, B., Hurwitz, M., Krebs, E.G., and Wigler, M. (1987) Cloning and characterization of BCY1, a locus encoding a regulatory subunit of the cyclic AMP-dependent protein kinase in Saccharomyces cerevisiae. Mol. Cell. Biol. 7:1371-1377.
19. Johnson, K.E., Cameron, S., Toda, T., Wigler, M., and Zoller, M.J. (1987) Expression in E. coli of BCY1, the regulatory subunit of cAMP-dependent protein kinase from Saccharomyces cerevisiae: purification and characterization. J. Biol. Chem. 262:8636-8642.
20. Scott, J.D., Glaccum, M.B., Zoller, M., Uhler, M.D., Helfman, D.M., McKnight, G.S., and Krebs, E.G. (1987) The molecular cloning of a type II regulatory subunit of cAMP-dependent protein kinase from rat skeletal muscle and mouse brain. Proc. Natl. Acad. Sci. USA 84:5192 5196.
21. Toda, T., Cameron, S., Sass, P., Zoller, M., and Wigler, M. (1987). Three different genes in S. cerevisiae encode the catalytic subunits of the cAMP-dependent protein kinase. Cell 50:277-287.
22. Rossi, J. and Zoller, M. Site-specific and regionally directed mutagenesis of protein-encoding sequences, pp. 51-63, in "Protein Engineering", (D. Oxender, ed.) Alan R. Liss, 1987.
23. Levin, L., Kuret, J., Johnson, K., Powers, S., Cameron, S., Michaeli, T., Wigler, M., and Zoller, M. (1988) A mutation in the catalytic subunit of yeast cAMP-dependent protein kinase tha disrupts regulation. Science 240:68-70.
24. Zoller, M., Johnson, K., Kuret, J., and Levin, L. (1988) Purification and characterization of C1, the catalytic subunit ofyeast cAMP-dependent protein kinase encoded by TPK1. Journal of Biological Chemistry 263:9142-9148.
25. Kuret, J., Johnson, K., Nicolette, C., and Zoller, M. (1988) Mutations in yeast R subunit that affect the interaction between regulatory subunit and catalytic subunit in yeast cAMP-dependen protein kinase. Journal of Biological Chemistry 263:9149-9154.
26. Cameron, S., Levin, L., Zoller, M. and Wigler, M. (1988) cAMP-independent control of sporulation, glycogen metabolism, and heat shock resistance in S. cereivisiae. Cell 53:555-566.
27. Levin, L. and Zoller, M.J. (1990) Association of subunits of cAMP-dependent protein kinase requires a negatively charged side group at a conserved threonine. Mol. Cell. Biol. 10:1066-1075.
28. Zoller, M.J., Yonemoto, W., Taylor, S.S. and Johnson, K.E. (1991) Mammalian cAMP-dependent protein kinase functionally replaces its yeast homolog. Gene 99: 171-179.
29. Gibbs, C.S. and Zoller, M.J. (1991) Rational scanning mutagenesis of a protein kinase indentifies functional regions involved in catalytic and substrate interactions. J. Biol. Chem. 266:8923-8931.
30. Zoller, M. J., (1991) "New molecular biology methods for protein engineering," Curr. Opinion Struct. Biol. 1: 605-610.
31. Gibbs, C.S. and Zoller, M.J. Identification of functional residues in proteins by charged-to-alanine scanning mutagenesis. Methods 3: 165-173 (1991).
32. Bennett, W. F., N. F. Paoni, B. A. Keyt, D. Botstein, A. J. S. Jones, L. Presta, F. M. Wurm, and M. J. Zoller. "High resolution analysis of functional determinants on human tissue-type plasminogen activator." J. Biol. Chem., 266: 5191-5201 (1991).
33. Gibbs, C.S. and Zoller, M.J. Identification of electrostatic interactions that determine the phosphorylation site specificity of the cAMP-dependent protein kinase from yeast. Biochemistry, 30: 5329-5334 (1991).
34. Gibbs, C.S., Knighton, D.R., Sowadski, J.M., Taylor, S.S., and Zoller, M.J. (1992) Systematic mutational analysis of cAMP-dependent protein kinase identifies unregulated catalytic subunits

and defines regions important for the recognition of the regulatory subunits. J. Biol. Chem. 267: 4806-4814 (1992).
35. Zoller, M.J. (1992) New molecular biology methods for protein engineering. Curr. Opin. Biotech.
36. Taylor, S.S., Knighton, D.R., Sowadski, J.M., Gibbs, C.S., and Zoller, M.J. (1993). A template for the protein kinase family. Trends Biochem. Sci. 18: 84-89.
37. Paoni, N.F., Chow, A.M., Pena, L.C., Keyt, B.A., Zoller, M.J., Bennett, W.F. Making tissue-type plasminogen activator more fibrin specific. Prot. Eng. 6: 529-534 (1993).
38. Rickles, R.J., Botfield, M.C., Weng, Z., Taylor, J.A., Green, O.M., Brugge, J.S., and Zoller, M.J. Identification of Src, Fyn, Lyn, PI3K, and Abl SH3 domain ligands using phage display libraries. Embo J. 13: 5598-5604 (1994).
39. Shiue, L., Green, O.M., Karas, J.L., Morgenstern, J.P., Ram, M.K., Taylor, M.K., Zoller, M.J., Zydowsky, L.D., Bolen, J.B., Brugge, J.S. Interaction of $p72^{syk}$ with the g and b subunits of the high-affinity receptor for immunoglobulin E, FceRI. Mol. Cell. Biol, 15: 272-281 (1995).
40. Shuie, L., Zoller, M.J. and Brugge, J.S. Activation of $p72^{syk}$ by phosphopeptides derived from the IgE receptor gamma and beta subunits. J. Biol Chem. 270: 10498-10502 (1995).
41. Narula, S.S., Yuan, R.W., Adams, S.E., Phillips, T.B., Zydowsky, L.D., Botfield, M.C., Hatada, M., Laird, E.R., Zoller, M.J., Karas, J.L., and Dalgarno, D.C. Solution structure of the carboxy-terminal SH2 domain of human tyrosine kinase Syk complexed with a phosphopentapeptide. Structure 3:1061-1073 (1995).
42. Rickles, R.J., Botfield, M.C., Zhou, X., Henry, P.A., Brugge, J.S., and Zoller, M.J. Phage display of ligand residues important for SH3 domain binding selectivity. Proc. Natl. Acad. Sci. USA. 92:10909-10913 (1995).
43. Hatada, M.H., Lu, X., Laird, E.R., Green, J., Morgenstern, J.P., Lou, M., Marr, C.S., Phillips, T.B., Ram, M.K., Thierault, K., Zoller, M.J., and Karas, J.K. Molecular basis for the interaction of the ZAP-70 protein tyrosine kinase with the T cell receptor. Nature 377: 32-38 (1995).
44. Rickles, R.J., Henry, P.A., Guan, W., Azimioara, M., Shakespeare, W.C., Violette, S., and Zoller, M.J. Chem. Biol. 5:529-538 (1998). A novel mechanism-based mammalian cell assay for the identification of SH2-domain-specific protein-protein inhibitors.
45. MacNeil, I. and Zoller, M.J. Emerging technologies for the discovery of small-molecule therapeutics. In Inflammation: Basic Principles and Clinical Correlation, J.I. Gallin and R. Snyderman, eds. Lippincott, Williams, and Wilkins, Philadelphia, (1999).
46. Li., X., Staszewski, L., Xu, H., Durick, K., Zoller, M., and Adler, E. Human Receptors for Sweet and Umami Taste. Proc. Natl. Acad. Sci. USA., 99:4692-4697 (2002).

TEXTBOOK

Watson, J. D., Gilman, M., Witkowski, J., and Zoller, M. "Recombinant DNA" WH Freeman, Inc., New York, 1992

PATENTS ISSUED

Anderson, S.A., Bennett, W.F., Botstein, D., Higgins, D.L., Paoni, N.F., and Zoller, M.J. Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,108,901.

Gill, J.F., Presta, L.G., Zoller, M.J. Tissue plasminogen activator having fibrin specific properties and deletion of amino acids 466-470, compositions and methods of treatment. US patent number 5,258,180.

Bennett, W.F,, Keyt, B.A., and Zoller, M.J. Tissue plasminogen activator variants with decreased clearance. US patent number 5,338,546.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J.Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,405,771.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J. Method for identifying tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,411,871.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J.Tissue plasminogen activator having zymogenic properties. US patent number 5,520,913.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J. Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,614,190.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J. Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,616,486.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J. Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,728,567.

Matthews, D.J., Wells, J.A., Zoller, M.J. Method of selection of proteolytic cleavage sites by directed evolution and phagemid display. US patent number 5,780,279.

Anderson, S., Bennett, W.F, Botstein, D., Higgins, D.L., Paoni, N.F., Zoller, M.J. Tissue plasminogen activator having zymogenic or fibrin specific properties. US patent number 5,840,564.

Matthews, D., Wells, J.A., and Zoller, M.J. Identification of novel substrates. US patent number 5,846,765.

Brugge, J., Morganstern, J., Shiue; L. , Zydowsky, L., Zoller, M. and Pawson, A. Human Syk. US patent number 5,981,262.

Lynch, B.A., MacNeil, I., and Zoller, M. In vitro fluorescence polarization assay. US patent number 6.207,397.

OTHER ACTIVITIES

Member of AAAS
Member Achems
Member Protein Society
Member of American Society for Biochemistry and Molecular Biology (ASBMB)
Member of American Chemical Society (ACS)
Editorial board of *Protein Engineering, Design and Selection (fka Protein Engineering)*